FORMULATION AND EVALUATION OF CLARITHROMYCIN FLOATING TABLET

Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
Chennai - 32

In partial fulfillment for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

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APRIL-2013

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1. INTRODUCTION

1.1 ORAL CONTROLLED DRUG DELIVERY SYSTEM

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance, and cost-effective manufacturing process.[1]

Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as.[2,3]

1) Drugs with short half-life requires frequent administration, which increases chances of missing dose of drug leading to poor patient compliance

2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult.

3) The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the CSS values fall or rise beyond the therapeutic range.

4) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.[4]

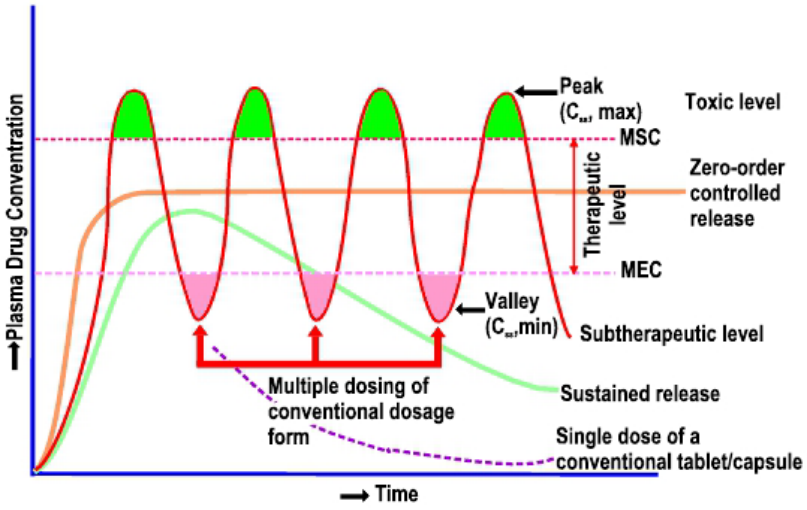


Fig.1: A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations.

Controlled Drug Delivery Systems:

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue.[5]

Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories.

1) Delayed release

2) Sustained release

3) Site-specific targeting

4) Receptor targeting

More precisely, controlled delivery can be defined as[6]

1) Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.

2) Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.

3) Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.

4) Provide a physiologically / therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/ therapeutic needs of the body.

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. Controlled drug delivery usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient.

Advantages of Controlled Drug Delivery System:

1. Avoid patient compliance problems.

2. Employ less total drug

a) Minimize or eliminate local side effects

b) Minimize or eliminate systemic side effects

c) Obtain less potentiation or reduction in drug activity with chronic use.

d) Minimize drug accumulation with chronic dosing.

3. Improve efficiency in treatment

a) Cures or controls condition more promptly.

b) Improves control of condition i.e., reduced fluctuation in drug level.

c) Improves bioavailability of some drugs.

d) Make use of special effects, E.g. Sustained-release aspirin for morning relief of arthritis by dosing before bed time.

4. Economy i.e. reduction in health care costs. The average cost of treatment over an extended time period may be less, with less frequency of dosing, enhanced therapeutic benefits and reduced side effects. The time required for health care personnel to dispense and administer the drug and monitor patient is also reduced.

Disadvantages:[7]

1) Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.

2) Poor in vitro – in vivo correlation.

3) Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus, increased risk of toxicity.

4) Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.

5) Reduced potential for dosage adjustment of drugs normally administered in varying strengths.

Oral Controlled Drug Delivery Systems:[8]

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage form (either solid, dispersion or

liquid), must be developed within the intrinsic characteristics of GI physiology. Therefore the scientific framework required for the successful development of an oral drug delivery systems consists of basic understanding of

(i) Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug;

(ii) The anatomic and physiologic characteristics of the gastrointestinal tract and

(iii) Physicochemical characteristics and the drug delivery mode of the dosage form to be designed.

The main areas of potential challenge in the development of oral controlled drug delivery systems are [9]

1) Development of a drug delivery system: To develop a viable oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for a duration required for optimal treatment.

2) Modulation of gastrointestinal transit time: To modulate the GI transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for a prolonged period of time to maximize the delivery of a drug dose.

3) Minimization of hepatic first pass elimination: If the drug to be delivered is subjected to extensive hepatic first-pass elimination, preventive measures should be devised to either bypass or minimize the extent of hepatic metabolic effect.

Conventional oral controlled dosage forms suffer from mainly two adversities.[10] The short gastric retention time (GRT) and unpredictable gastric emptying time (GET). A relatively brief GI transit time of most drug products impedes the formulation of single daily dosage forms. These problems can be overwhelmed by altering the gastric emptying. Therefore it is desirable, to formulate a controlled release dosage form that gives an extended GI residence time.

Extended release dosage form with prolonged residence time in stomach are highly desirable for drugs.[11,12]

i) That are locally active in stomach,

ii) That have an absorption window in the stomach or in the upper small intestine,

iii) That are unstable in the intestinal or colonic environment,

iv) Have low solubility at high pH values.

1.2 Gastro retentive Dosage Form (GRDF):

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDF or GRDS).[13]

GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form.[14]

Dosage form with prolonged GRT, i.e. gastro retentive dosage forms (GRDF), will bring about new and important therapeutic options such as[15]

1) This application is especially effective in sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To override this problem, erodible, gastro retentive dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site.

2) GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa. (For e.g. Eradicating Helicobacter pylori from the submucosal tissue of stomach) making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis, reduce the risk of gastric carcinoma and administer non-systemic controlled release antacid formulations (calcium carbonate).

3) GRDFs can be used as carriers for drugs with so-called absorption windows. These substances for e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides, tetracyclines etc.), are taken up only from very specific sites of the GI mucosa.

1.3 BIOLOGICAL ASPECTS OF GRDFs:

Role of GI tract: Stomach[16,17]

The stomach is J-shaped organ located in the upper left hand portion of the abdomen, just below the diaphragm. It occupies a portion of the epigastric and left hydrochondriac region. The main function of the stomach is to store the food

temporarily, grind it and then release it slowly into the duodenum. Due to its small surface area very little absorption takes place from the stomach. It provides barrier to the delivery of drugs to small intestine.

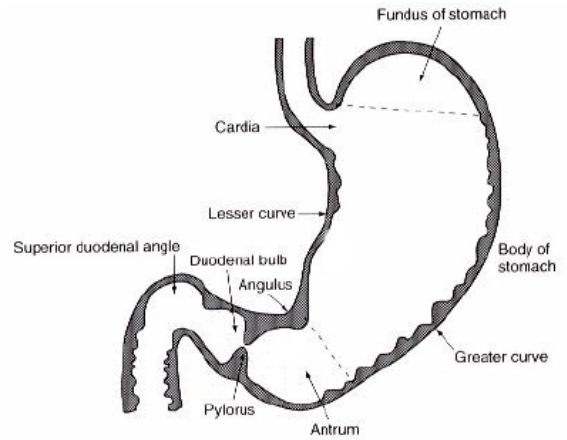


Fig.2: Anatomy of Stomach

The stomach is divided into three anatomical regions. I)Fundus ii) Body and iii) Pylorus (or antrum). The proximal stomach consisted of fundus and body, which serves as a reservoir for ingested materials, whereas the distal region (pylorus) is the major site of mixing motions, acting as a pump to propel gastric contents for gastric emptying. Gastric emptying occurs both in fasting as well as fed states.

The GI tract is always in a state of continuous motility. There are two modes of motility pattern. The digestive mode and interdigestive mode. In case of fasted state an interdigestive series of electrical events occurs in cyclic manner both through stomach and small intestine every 2-3 hr. This electrical activity is termed as interdigestive myoelectric cycle or migrating myoelectric complex (MMC), which is further divided into four phases.[18,19]

Phase I : Period of no contraction.

Phase II : Period of intermittent contraction.

Phase III : Period of regular contractions at the maximal frequency that migrate distally.

Phase IV : Period of transition between phase III and phase I.

Phase III has a housekeeping role and serves to clear all indigestible materials from the stomach and small intestine. Consequently, a controlled-release gastrointestinal drug delivery system must be capable of resisting the house keeping action of phase III. Studies revealed that in the fed state, the gastric emptying rate is slowed since the onset of MMC is delayed. It can be concluded that feeding results in a lag time before onset of gastric emptying cycle.

1.4 APPROACHES TO GASTRIC RETENTION[20]

A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts. These include–

a) Floating Systems:

Floating Drug Delivery Systems (FDDS) [21] have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system.

After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations

in the plasma drug concentrations. Floating systems can be classified into two distinct categories, non-effervescent and effervescent systems.

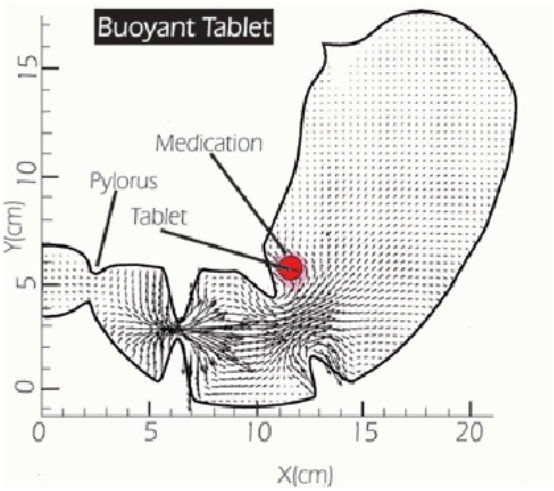


Fig. 3: Graphic of Buoyant tablet which is less dense than the stomach fluid and therefore remains in the fundus.

b) Bio/Muco-adhesive Systems:[22]

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the GRT of drug delivery system (DDS) in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane.

The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bio/muco-adhesive polymers. The ability to provide adhesion of a drug (or a delivery system) to the GI wall provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect.

Binding of polymers to the mucin/epithelial surface can be divided into three broad categories :–

Hydration-mediated adhesion.

Bonding-mediated adhesion.

Receptor-mediated adhesion.

c) Swelling and Expanding Systems:[23]

These are the dosage forms, which after swallowing, swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as "plug type system", since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity. Such polymeric matrices remain in the gastric cavity for several hours even in the fed state.

A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for prolonged period.

d) High Density Systems:[24]

These systems with a density of about 3 gm/cm^3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of

2.6-2.8 g/cm^3 acts as a threshold value after which such systems can be retained in the lower part of the stomach. High-density formulations include coated pellets.

Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc. They are retained in the antrum of stomach as shown in Fig. 4.

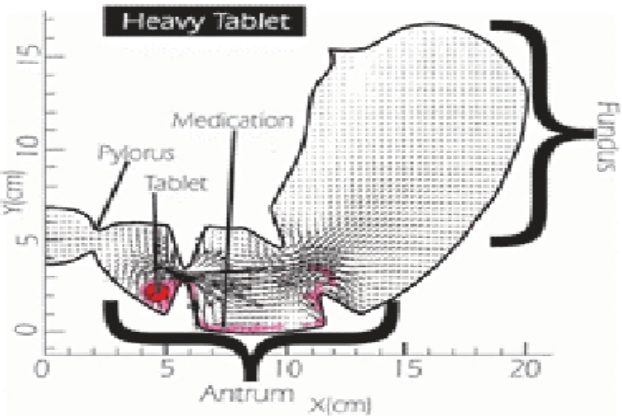


Fig. 4: Graphic of heavy tablet which is denser than the stomach fluid and therefore sinks to the antrum.

e) Incorporation of Passage Delaying Food Agents:-[25]

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of the stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in the gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C10-C14.

f) Ion Exchange Resins:[26]

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange

resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

g) Osmotic Regulated Systems:[10]

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment.

1.5 TYPES OF FLOATING DRUG DELIVERY SYSTEMS (FDDS)[27,28]

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are :

A. Effervescent System, and

B. Non- Effervescent System.

A. EFFERVESCENT SYSTEM:-

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature.

These effervescent systems further classified into two types.

I. Gas Generating systems

II. Volatile Liquid/Vacuum Containing Systems.

I. Gas – Generating Systems:

1. Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced Sysem (HBS):

These are as shown in Fig.5 and formulated by intimately mixing the CO_2 generating agents and the drug with in the matrix tablet.

These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

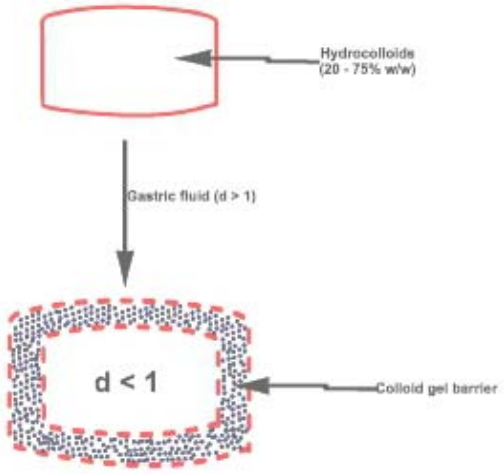


Fig. 5: Intra Gastric Single Layer Floating Tablet.

2. Intra Gastric Bilayer Floating Tablets:

These are also compressed tablet as shown in Fig 6 and containing two layer i.e.,

i. Immediate release layer and

ii. Sustained release layer.

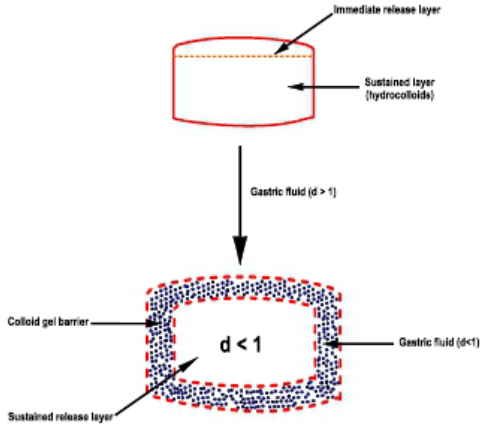


Fig. 6: Intra Gastric Bilayer Floating Tablet.

3. Multiple Unit type floating pills:

These system consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consist of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO2 within the system.

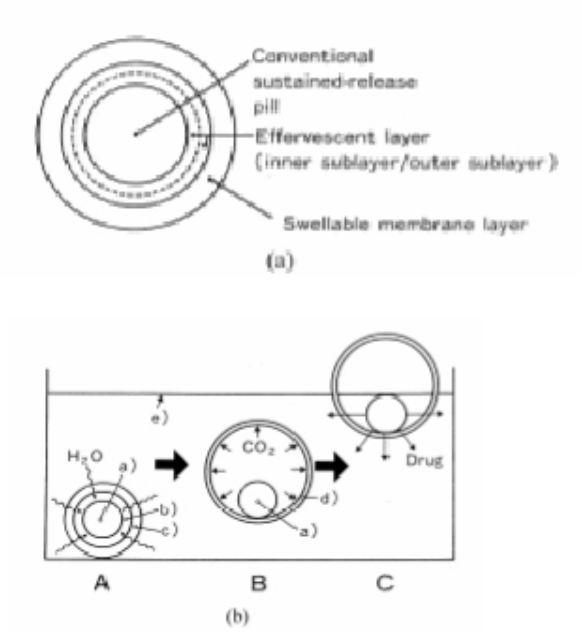


Fig. 7: (a) A multi-unit oral floating dosage system. (b) Stages of floating mechanism: (A) penetration of water; (B) generation of CO2 and floating; (C) dissolution of drug. Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker (37^0C).

II. Volatile Liquid / Vacuum Containing Systems:

1. Intragastric Floating Gastrointestinal Drug Delivery System:

These system can be made to float in the stomach because of floatation chamber, which may be a vacum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microprous compartment, as shown in Fig.8.

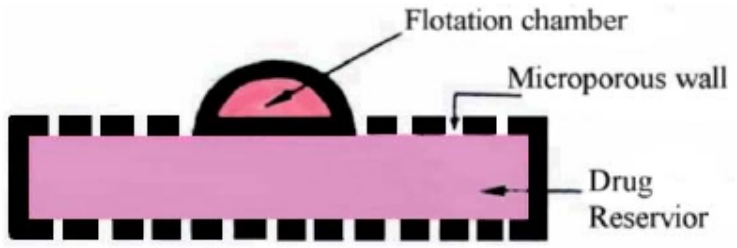


Fig. 8: Intra Gastric Floating Gastrointestinal Drug Delivery Device

2. Inflatable Gastrointestinal Delivery Systems:

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid.

This system is shown in Fig. 9.

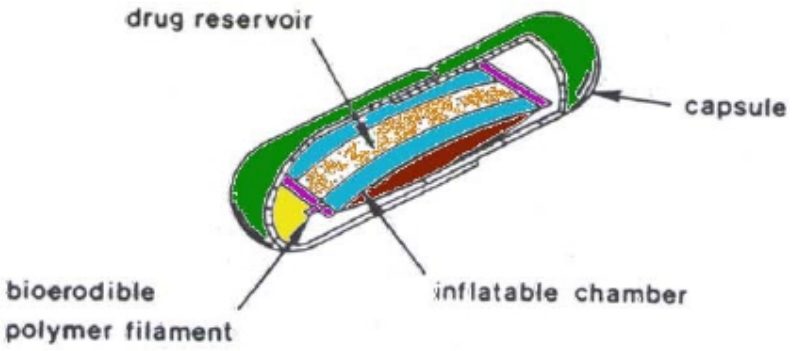


Fig. 9: Inflatable Gastrointestinal Delivery System

3. Intragastric Osmotically Controlled Drug Delivery System:

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastirc osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consist of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug

reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice.

The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach. This system is shown in Fig. 10.

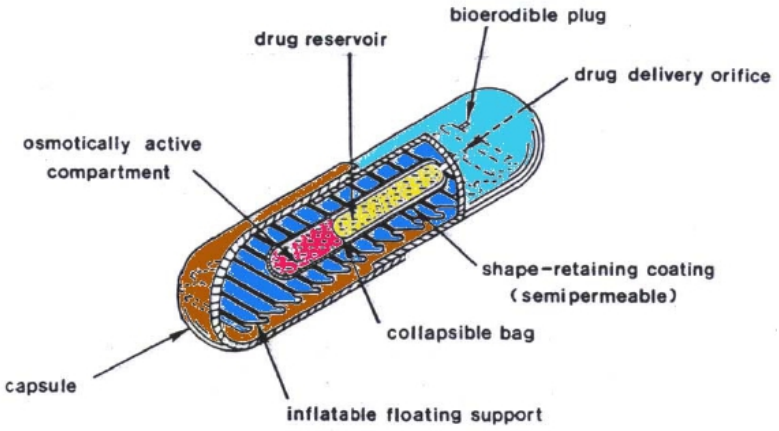


Fig. 10: Intragastric Osmotically Controlled Drug Delivery System

B. NON EFFERVESCENT SYSTEMS:

The Non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol. The various types of this system are as:

1. Single Layer Floating Tablets:

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

2. Bilayer Floating Tablets:

A bilayer tablet contain two layer one immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

3. Alignate Beads:

Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, these floating beads gave a prolonged residence time of more than 5.5 hour.

4. Hollow Microspheres:

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol:dichloromethane solution of the drug and an enteric acrylic polymer was

poured into an agitated aqueous solution of PVA that was thermally controlled at 400C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug.

The microballoons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours in vitro.

1.6 Factors Controlling Gastric Retention Time of Dosage Form:[29]

The gastric retention time (GRT) of dosage form is controlled by several factors, that affect their efficacy as a gastroretentive system.

- Density – GRT is a function of dosage form buoyancy that is dependent on the density.[30]
- Size – Dosage form units with a diameter of more than 9.5mm are reported to have an increased GRT.[31]
- Shape of dosage form – Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilopounds per square inch (KSI) are reported to have better GRT. 90% to 100% retention at 24 hours compared with other shapes.
- Single or multiple unit formulation – Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
- Fed or unfed state – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex

(MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

- Nature of meal – Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.[32]

- Caloric content – GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

- Frequency of feed – The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

- Gender – Mean ambulatory GRT in males (3.4□0.6 hours) is less compared with their age and race-matched female counterparts (4.6□1.2 hours), regardless of the weight, height and body surface.

- Age – Elderly people, especially those over 70, have a significantly longer GRT.

- Posture – GRT can vary between supine and upright ambulatory states of the patient.[33]

- Concomitant drug administration – Anticholinergics like Atropine and Propantheline, opiates like Codeine and prokinetic agents like Metoclopramide and Cisapride.
- Biological factors – Diabetes and Crohn's disease.

1.7 Advantages of FDDS:

Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include:

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
2. Controlled delivery of drugs.
3. Delivery of drugs for local action in the stomach.
4. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
5. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
6. Simple and conventional equipment for manufacture.
7. Ease of administration and better patient compliance.
8. Site-specific drug delivery.

Disadvantages of FDDS:[34]

1. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.

2. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.

3. High variability in gastric emptying time due to its all or non-emptying process.

4. Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diametral size. Therefore patients should not be dosed with floating forms just before going to bed.

List of Drugs along with Floatable Drug Delivery Systems:

SR. NO.	DOSAGE FORM	DRUGS
1	Microspheres	Aspirin, Grisiofulvin, p-nitroanilline, Ibuprofen, Terfinadine, Tranilast.
2	Granules	Diclofenac sodium, Indomethacin, Predmisolone
3	Films	Cinnarizine
4	Powders	Several basic drugs
5	Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, 1-Dopa, benserazide, Misoprostol, Propranolol HCl, Ursodeoxycholic acid
6	Tablets/pills	Acetaminophen, Acetylsalisylic acid, Amoxicillin trihydrate, Ampicillin, Atenolol, Chlorpheniramine, Cinnazirine, Diltiazem, Fluorouracil, Isosorbide mononitrate, Isosorbide dinitrate, p-aminobenzoic acid, Piretanide, Prednisolone, Quinidine gluconate, Riboflavin-5-phosphate, Sotalol, Theophylline, Verapamil HCl

1.8 Marketed Products of FDDS:

SR. NO.	BRAND NAME	DRUG (DOSE)	COMPANY, COUNTRY	REMARKS
1.	® Modapar	Levodopa (100 mg), Benserazide (25 mg)	Roche Products, USA	Floating CR capsule
2.	® Valrelease	Diazepam (15 mg)	Hoffmann-LaRoche, USA	Floating capsule
3.	Liquid ® Gavison	Al hydroxide (95 mg), Mg carbonate (358 mg)	Glaxo Smith Kline, India	Effervescent floating liquid alginate preparation
4.	® Topalkan	Al-Mg antacid	Pierre Fabre Drug, France	Floating liquid alginate preparation
5.	Conviron	Ferrous sulphate	Ranbaxy, India	Colloidal gel Forming FDDS
6.	® Cifran OD	Ciprofloxacin (1 gm)	Ranbaxy, India	Gas-generating floating tablet
7.	® Cytotec	Misoprostal (100 mcg/200 mcg)	Pharmacia, USA	Bilayer floating capsule
8.	Oflin OD®	Ofloxacin (400mg)	Ranbaxy, India	Gas generating floating tablet

Disease Profile

In the present study Clarithromycin is taken as a model drug for the development of formulation of Hydrodynamically balanced tablets. Clarithromycin is one of the main antibiotic in the first line treatment of H.pylori infection.

H.pylori is the most common bacterial pathogen responsible for causing peptic ulcer and gastritis. Helicobacter pylori is a motile, aerobic, S-shaped bacterium that is typically found in the gastric epithelium of the antrum. The organism possesses flagellae that are important in its ability to penetrate the mucus layer of gastric mucus. It produces a powerful urease that generates an alkaline microenvironment to survive gastric acidity.

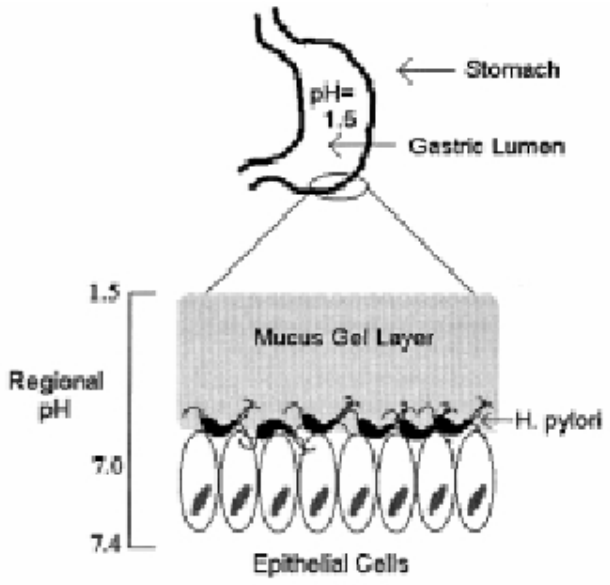


Fig. 11: Schematics of H.pylori location within the stomach.

The eradication of H.pylori is limited by its unique characteristics i.e. it penetrates the gastric mucus layer and fixes itself to various phospholipids and glycolipids on epithelial surface. Thus the microorganism exclusively resides on the

luminal surface of the gastric mucosa under the mucus gel layer in the acidic environment of the gut. H.pylori is equipped with catalase and urease enzymes, which breakdown urea into bicarbonate and ammonia and thus in turn protects the bacterium in the acid milieu of stomach vis-à-vis leads to gastric epithelial injury.[35]

For effective treatment of H.pylori infection, therapeutic agents have to penetrate the gastric mucus layer to disrupt and resist the mechanism of colonization,[36,37] which needs targeted drug delivery within the stomach environment.

This stomach-specific delivery system will increase the gastric residence time, decrease the diffusional distance, and allow more of the antibiotic to penetrate through the gastric mucus layer and act locally at the infectious site.

By increasing the local concentration and contact time, stomach specific delivery system also minimize the resistance problems associated with systemic administration of antibiotics.[38,39,40]

Classifiction Of Antibacterial:

i) Antibacterial are classified in many ways based on chemical structure;its spectrum of activity;Pharmacological activity.

a) β-lactum antibiotic:eg.penicillins,Cephalosporins,
b) Aminoglycosideantibiotics:eg.Neomycin,Streptomyci
c) Tetracyclines:eg.Tetracycline,Oxytetracycline.
d) Macrolide antibiotics:eg.Clarythromycin,Erythromycin.
e) Lincomycin:eg.Lincomycin,Clindamycin
f) miscellaneous:eg.Novobiocin,Chloramphenicol.

ii) Based on pharmacological activity

a)Antifungal antibiotics.

i)Polyene:eg.amphotericin B, nystain.

ii)others:eg.Griseofulvin.

b)anticancer Antibiotics:eg.Streptozocin,Valrubicin.

c)Antityphoid antibiotic:eg.Chloramphenicol.

d)Antidiarrheal antibiotic:eg.Colistin

e)Antituberculer antibiotic:eg.Rifampicin,Cycloserine.

2. REVIEW OF LITERATURE

REPORTED FLOATING DRUG DELIVERY SYSTEMS

A lot of work has been done on the development of floating drug delivery system. Some of them are cited below.

Ichikawa M, et al.[47] reported a multiple unit type of floating dosage form containing Aminobenzoic acid for which the floating ability and sustained release characteristics were evaluated in-vitro. The system was floating completely within ten minutes and about 80% remained floating over 5 hours, irrespective of pH and viscosity of the buffer medium used, and followed zero order drug release.

Floating force kinetics of peroral polymeric matrix dosage forms by a novel in-vitro resultant-weight measuring system were reported by

Timmermans J. et al.[48] showed that bulk density of dosage form was not the most appropriate parameter for describing its buoyancy capabilities. These capabilities were perfectly represented and monitored by resultant weight measurements.

Results indicated that the magnitude of floating strength may vary as a function of time and usually decreases after immersion of the dosage form into the fluid consequently to the evolution of its hydrodynamic equilibrium.

Baumgartner S, et al.[49] developed floating matrix tablets containing Hydroxypropyl Methyl Cellulose, which after oral administration are designed to prolong the gastric residence time, increase the bioavailability and diminish the side effects of irritating drugs. The importance of the composition optimization, the formulation aspects and characterization of the tablets were examined. The

investigation showed that the tablet composition and mechanical strength have great influence on the floating and drug release properties of the tablets. They concluded that the drug release from the tablets followed non-Fickian transport.

Roughe N, et al.[50] conducted a study to evaluate the factors that improves the in vitro buoyancy and drug release profile of floating minitablets containing either Piretinide or Atenolol as the model drug. The buoyancy of the minitablets was achieved either by the swelling of the excipients or by incorporating gas generating agent, sodium bicarbonate. The study concluded that it is possible to produce minitablets containing either Piretinide or Atenolol, which have a positive resultant weight during more than 6 hr and satisfactory release profiles.

Ingani HM, et al.[51] described the formulation, dissolution, buoyancy and in vivo release tests of a double layer, sustained release Riboflavin phosphate sodium hydrophosphate matrix oral tablet containing a carbon dioxide generating layer.

The in vivo behavior of this floating tablet was then compared to a classical hydrodynamically balanced capsule system. The floating dosage forms had increased residence time as compared to the non-floating tablet.

Menon A, et al.[52] reported the formulation of a monolithic floating dosage form for Furosemide using factorial design keeping the drug to polymer ratio, polymer to polymer ratio and polymer grade as the three factors. The optimized formulation thus obtained was found to have a good in vitro / in vivo correlation.

Shoufeng Li, et al.[53] developed an optimized gastric floating drug delivery system for oral controlled delivery of Calcium. A central, composite Box-Wilson design for the controlled release of calcium was used with three formulation variables;

HPMC loading, citric acid loading and magnesium stearate loading. All three formulation variables were found to significantly effect release properties. Only HPMC loading was found to be significant for floating properties.

Hilton AK, et al.[54] fabricated an oral sustained release floating tablets of Amoxycillin trihydrate and carried out the in vitro – in vivo evaluation. From the studies, it shows that the drug slowly released in the stomach by diffusion from the floating matrix tablet and then trickle towards the proximal intestine where absorption occurs. It improved the delivery of antibiotic resulting in more uniform levels of antibiotic following less frequent oral dosing.

Ozdemir N, et al.[55] developed floating bilayer tablet of Furosemide-cyclodextrin inclusion complex. They determined the gastric residence time using radiographs by adding BaSO4 and reported that the tablet stayed in stomach for 6 hours. Also the bioavailability of Furosemide from floating tablet was about 1.8 times those of the conventional tablet and also significant in vitro – in vivo correlation was detected.

Jimenez-Castellanos, et al.[22] designed and tested the in vitro floating and bioadhesive property of Sotalol for oral application. Tablets were prepared by mixing the active ingredient with Sodium carboxy methyl cellulose, Hydroxy propyl cellulose and a carbonate to generate gas. In vitro tests for release of drug, floatation

and bioadhesion of the tablets were carried out. They concluded that this system showed good characteristics for controlled drug delivery system.

El-Kamel.[56] developed a sustained release system for Ketoprofen to increase its residence time in the stomach without contact with the mucosa and was achieved through the preparation of floating microparticles by the emulsion solvent diffusion technique. All the floating microparticle formulation were evaluated for flow properties, packability and drug release rate.

Joseph NJ, et al.[57] studied the effect of solvent evaporation technique on floating type hollow polycarbonate microsphere of Piroxicam which were capable of floating on simulated gastric fluid. Pharmacokinetic analysis showed that the bioavailability of Piroxicam hollow microsphere was about 1.4 times that of free drug and was about 4.3 times for the dosage form consisting of microsphere plus the loading dose. The elimination half life was increased by three times that of free drug.

Park, et al.[58] developed and evaluated floating beads from Sodium Alginate solution containing CaCO3 or NaHCO3 as gas-forming agents with Riboflavin as a model drug. In vitro release studies revealed that CaCO3 is superior to NaHCO3 as gas forming agent in alginate bead preparations, with enhanced buoyancy and sustained release properties making them excellent for floating drug delivery system.

Burns SJ, et al.[59] reported an in-vitro dissolution method for a floating dosage form with biphasic release characteristics. A modified paddle dissolution for the evaluation of Propranolol in a floating dosage form that demonstrates both rapid and sustained release properties were reported.

Machida S, et al,[60] fabricated two drug formulations which floated in gastric juice. One, a buoyant tablet, consisted of powdered Soyabean protein, drug and Sodium bicarbonate. The other, a laminated film type preparation consisted of a drug film, an effervescing film containing Sodium bicarbonate and outer drug release regulating time. Cinnarazine, an acid soluble drug was used as the model drug.

Deshpande AA, et al.[21] developed novel controlled release gastric retention system, which consists of a matrix tablet, coated with a permeable membrane. Tablets containing soluble drug Chlorpheniramine maleate and poorly soluble drug Riboflavin were compressed. Studies showed that, the chances of elimination through the pylorus greatly reduced due to tablets expansion and the tablet expelled out of stomach at the end of the drug release.

Blanquet S, et al.[61] developed a dynamic artificial gastrointestinal system for studying the behaviour of orally administered drug dosage form under various physiological conditions. It was studied using two model drugs Paracetamol and Acetaminophen. The results concluded that the in-vitro results were consistent with in vivo data.

Shah S, et al.[62] developed stomach specific drug delivery for treatment of Helicobacter pylori consisted of Tetracycline loaded chitosan microsphere which release drug for a period of 12 hr residing the dosage form in stomach due to inherent properties of chitosan to form a gel in acidic medium as well as bioadhesion characteristics.

Alderete ME, et al.[63] prepared matrix tablets of Metranidazole with HPMC viscosity ranging from 15cps to 30,000 cps and particle size ranging from 163 m to 505 m. There was a linear relationship between the inverse of release rate and viscosity grade at polymer concentration of 10%. A linear relationship between the release rate and cube of the diameter particle size also determined.

El-Gibaly[64] formulated and compared chitosan floating microcapsules containing Melatonin with conventional non-floating Chitosan microspheres. Floating microcapsules showed zero order release kinetics and more than 12 hrs floating time in vitro. Moreover, these floating microcapsules greatly retarded the drug release lasting for several hours while it was almost instant from conventional microspheres.

A new intragastric delivery system for the treatment of H.pylori associated gastric ulcer was developed by **yang and hejazi** They developed intragastric floating drug delivery system by using HPMC K4M, Chitosan and found that the developed delivery system has potential to increase the efficacy of the therapy and improve patient compliance.

Bhat SS, et al.[65] developed Clarithromycin sustained release tablet for improved efficacy. They observed that, in sustained release formulation, the concentration of antibiotic is far greater than MIC and reduced the drug resistance. Statistical analysis showed that drug release from the tablet matrix followed zero order kinetics.

Pharmacokinetic parameters of Clarithromycin and its metabolite were studied by

Scaglione et al.[66] and found that maximum serum concentrations were reached within 3 hours irrespective of ethnic origin and regardless of the dose. The presence of food have no clinical effect on Clarithromycin pharmacokinetic properties.

Darkes MJM, et al.[67] developed Clarithromycin extended release tablet. It showed that maximum plasma concentration are lower and reached later with extended-release tablets than with the immediate release tablets.

3. AIM AND OBJECTIVE

H.pylori is currently the single most common cause of peptic ulcer worldwide, accounting for 80% gastric ulcer and up to 95% of duodenal ulcers. Antimicrobial therapy is most acceptable choice of treatment for patients with active gastric or duodenal ulcers who are infected with H.pylori.

Although H.pylori is sensitive to antimicrobial agents *in-vitro*, successful treatment of infection is challenging due to its unique. Characteristics, i.e., the bacterium tends to inhabit the gastric mucous gel and hence access for antimicrobial drug to the site of infection is restricted, both from the lumen of the stomach and from the gastric blood supply.

Therefore for effective treatment, the therapeutic agents have to penetrate the gastric mucus layer to disrupt the mechanism of colonization, within the stomach environment. One way to improve the efficacy of eradicating H.pylori infection is to deliver the antibiotic locally to the stomach.

This goal can be achieved by the development of hydrodynamically balanced system or floating drug delivery system which increases the gastric residence time, decreases the diffusional distance and allow more of the antibiotic to penetrate through the gastric mucus layer and act locally at the infectious site. Clarithromycin is one of the first line antibiotic in the treatment of H.pylori infection along with Amoxycillin and Omeprazole.

The present study outlines a systematic approach for design and development of hydrodynamically balanced tablets of clarithromycin to enhance the bioavailability and therapeutic efficacy of the drug.

OBJECTIVE OF THE STUDY

- Design and development of the Hydrodynamically balanced tablets of Clarithromycin.
- To study the effect of different polymers on the drug release.
- Evaluation of the prepared formulation for physicochemical properties and drug release profile.
- Analyse the drug release data for kinetic equations.

4. PLAN OF WORK

1. Preformulation Study
    - Organoleptic properties
    - Solubility
    - Determination of melting point
    - Compressibility index
    - pH
    - Loss on drying
2. Evaluation of Powders
    - Angle of repose
    - Bulk density
    - Tapped density
    - Powder flow Properties
3. Compression of powders into tablet
4. Tablet evaluation
    - Thickness
    - Hardness
    - Friability
    - Uniformity of weight
    - Drug content

- Tablet density
- *In vitro* buoyancy studies
- *In vitro* dissolution

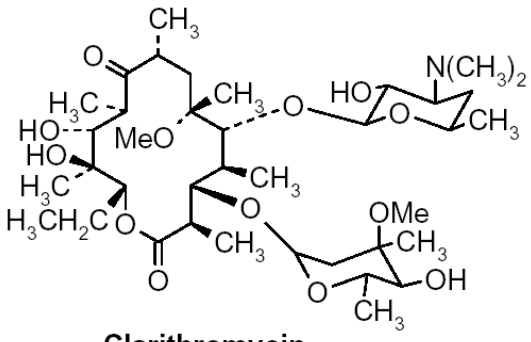
5. Kinetic Studies
6. Stability Studies

5. PROFILE

5.1 DRUG PROFILE

CLARITHROMYCIN[41,42]

Structure:



Clarithromycin

Chemical Name : 6-O-methylerythromycin

Empirical formula : $C_{38}H_{69}NO_{13}$

Molecular Weight : 747.95

Melting Point : 220^0C

Description : White or colourless, odourless crystals.

Category : Antibacterial

Storage : Store in a cool, dry place.

Solubility:

It is soluble in chloroform, acetone, dilute acids. Slightly soluble in methanol, ethanol and acetonitrile, and practically insoluble in water.

Pharmacodynamic Property:

Clarithromycin is a semi-synthetic broad spectrum macrolide antimicrobial agent structurally related to Erythromycin. It is acid stable and rapidly absorbed after oral administration.

Clarithromycin is bacteriostatic or bacteriocidal depending on the organism and antimicrobial agent concentration. It exerts its antibacterial action by binding to the 50S ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. It is highly potent against wide variety of aerobic and anaerobic gram-positive and gram-negative organisms such as S.aureus, S.pneumoniae, H.influenza, Moraxella catarrhalis, and other microorganisms like Mycobacterium avium complex (MAC) and Helicobacter pylori.

Pharmacokinetic Property:

Absorption:- Clarithromycin is absorbed rapidly from the gastrointestinal tract after oral administration. The microbiologically active metabolite 14-hydroxy Clarithromycin is formed by first pass metabolism. Peak concentration occurs approximately 2 hrs after drug administration. Steady state peak concentration in plasma are 2 to 3 mg/ml after 2 hours from a regimen of 500mg every 12 hours or 2 to 4 hours after two 500mg extended release tablets given orally.

Distribution:-

Clarithromycin and its active metabolite 14-hydroxy Clarithromycin distribute widely throughout the body and achieve high intracellular concentrations. Tissue concentrations generally exceed serum concentrations. Concentrations in middle ear fluid are 50% higher than simultaneous serum concentrations for both

Clarithromycin and the active metabolite. Protein binding of Clarithromycin ranges from 40-70%.

Elimination:-

Clarithromycin is eliminated by renal and non-renal mechanisms. It is metabolized in the liver to active 14-hydroxy metabolite. The elimination half-lives of Clarithromycin and 14-hydroxyclarithromycin are approximately 3 to 7 hours and 5 to 9 hours. The amount of Clarithromycin excreted unchanged in the urine ranges from 20% to 40% depending on the dose administered and formulation.

Therapeutic Uses:

- Used in combination for the treatment of Helicobacter pylori infection and duodenal ulcer disease.
- For treatment of upper and lower respiratory tract infections.
- For prevention of disseminated Mycobacterium avium complex (MAC) infections in patients with advanced human immunodeficiency virus (HIV) infections.
- Uncomplicated skin and skin structure infections like Folliculitis, Cellulitis, Erysipelas.

Adverse Effects:

The majority of the adverse effects reported were of mild and transient nature like Diarrhoea, nausea, abnormal taste, dyspepsia, headache, etc.

Dosage and Administration:

Clarithromycin is used orally in a dose of 250 to 500mg twice daily.

Marketed Preparations:

CELEX OD (Abott) 500 mg

Clarithro ER (Alembic) 500 mg

URCLAR OD (Novartis) 500 mg

MACLAR (Gracewell) 500 mg

Mechanism Of Action:

a) clarithromycin prevents bacteria from growing by interfering with their Protein synthesis.

b) clarithromycin binds to the subunit 50S of the bacterial ribosome and thus inhibits the translation of Peptides

c) Clarithromycin has similar antimicrobial spectrum as erythromycin but is more effective against certain gram-negative bacteria, particularly Legionella Pneumophilla.

d) Clarithromycin also has bactericidal effect on certain strains such as Haemophilus Influenzae, Streptococcus Pneumoniae and Neisseria Gonorrhoae.

5.2. POLYMER REVIEW

5.2.1 HYDROXY PROPYL METHYL CELLULOSE[43]

Non-proprietary names:

BP : Hypromellose

USP : Hydroxy propyl methyl cellulose

Synonyms:

Methyl hydroxypropyl cellulose, Propylene glycol ether of methylecellulose, Methylcellulose, Methylcellulose propylene glycol ether.

Chemical Name:

Cellulose, 2-hydroxypropyl methyl ether

Empirical formula:

$C_8H_{15}O_6 – (C_{10}H_{18}O_6)n – C_8H_{15}O_5$

Description:

It occurs as odourless and tasteless creamy white coloured fibrous or glandular powder.

Molecular weight:-

Approximately 86,000

Functional category:-

Coating agent, film former, Tablet binder, Stabilizing agent, Suspending agent, Viscosity increasing agent.

Density:

0.25 – 0.70 g/cm3

Solubility:

Soluble in cold water forming viscous colloidal solution, insoluble in Chloroform, Ethanol and Ether, but soluble in mixtures of Ethanol and Methylene chloride.

Viscosity:

HPMC K4M : 4,000 cps

HPMC K15M : 15,000 cps

Stability and Storage:

It is stable although it is slightly hygroscopic. The bulk material should be stored in a air tight container in a cold and dry place. Increase in temperature reduces the viscosity of the solution.

Safety:

It is widely used in many oral and topical pharmaceutical formulations. It is generally regarded as a non-toxic and non-irritant material, although excessive consumption may have laxative effect.

Pharmaceutical Applications:

1. Film-former in tablet film coating: Lower viscosity grades are used in aqueous film coating and higher viscosity grades are used in solvent film coating.

2. Binder in tablet granulations: 2.5% high-viscosity grades are used to retard the release of water-soluble drugs.

3. As a Thickening agent: Thickening agent added to vehicles for eye drops & artificial fear solutions at 0.45 - 1.0% concentrations.

4. As a protective colloid : Prevents droplets and particles from

5. Coalescing or agglomerating, thus inhibiting the formation of sediments. It is used as emulsifier, suspending agent & stabilizer in gels & ointments. As an adhesive in plastic bandages.

5.2.2 CHITOSAN[44,45,46]

Chitosan is obtained by alkaline deacetylation of chitin, the most abundant polysaccharide in nature. The two polymers are distinguished by insolubility or solubility in dilute aqueous acid solution. Main source of chitin are the shell wastes of shrimp, lobster and crab.

Chemical name:

Poly(N-acetyl-2-amio-2-deoxy-D-glucopyranose)

Molecular Weight:

50,000 – 20,00,000

Category:

Tablet binder, wetting agent, coating agent, also used in vaccine delivery, peptide delivery, gene delivery.

Description:

Odourless, tasteless, white or creamy white fibers.

Density:

1.35 – 1.40 g/cm3

Solubility:

Soluble in dilute acid solutions, insoluble in alkaline solution, water and most organic solvents.

Viscosity:

Chitosan A (49%)

Chitosan B (66%) medium viscosity type.

Stability and Storage:

Stable in dry form. Store in a well closed container in a cool place.

Safety:

It is non-toxic, biodegradable and biocompatible. It has antiulcerogenic, mucoadhesive property.

5.3 EXCIPIENT REVIEW

5.3.1 SODIUM BICARBONATE[43]

Non-proprietary Names:

BP/EP: Sodium bicarbonate

Synonym:

Baking soda, E-500, Monosodium carbonate.

Chemical name:

Carbonic acid, Monosodium salt, Monosodium carbonate.

Empirical formula: $NaHCO_3$

Molecular weight: 84.01

Category:

Alkalizing agent, therapeutic agent.

Description:

It is an odourless, white crystalline powder with slight alkaline taste.

Acidity/ Alkalinity:

pH 8.3 for freshly prepared 0.1M aqueous solution at 250^0C.

Density:

2.159 g/cm3

Solubility:

Soluble in water, practically insoluble in ethanol.

Stability and Storage:

Sodium bicarbonate is stable in dry air but slowly decomposes in moist air and should therefore be stored in well-closed container in a cool dry place.

Safety:

Orally ingested sodium bicarbonate neutralizes gastric acid with the evolution of carbon dioxide and may cause stomach cramps and flatulence.

5.3.2 MAGNESIUM STEARATE[43]

Non-proprietary Names:

BP: Magnesium stearate

Synonyms:

Metallic stearate, Magnesium salt.

Chemical name:

Octadecanoic acid, Magnesium salt.

Empirical formula **:** $C_{36}H_{70}MgO_4$

Molecular weight **:** 591.27

Category **:** Tablet and capsule lubricant (0.25 – 5.0%)

Description:

Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, the powder is greasy to touch and readily adheres to the skin.

Density:

1.03 to 1.08 g/cm3

Solubility:

Insoluble in ethanol (95%) and water. Slightly soluble in warm benzene and hot alcohol.

Stability and storage:

It is stable and to be stored in a well closed container in a cool dry place.

Safety:

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being non-toxic following oral administration. Inhalation of magnesium stearate is harmful.

5.3.3 LACTOSE[43]

Non-proprietary name:

BP/EP : Lactose

Synonym **:** Milk sugar, Saccharum lactis.

Chemical name **:** 4-O-â-D-galactopyranosyl-á-D-glucopyranose

4-(â-D-galactoside)-D-glucose

Empirical formula **:** $C_{12}H_{22}O_{11}$

$C_{12}H_{22}O_{11}H_{20}$

Molecular weight **:** 342.30 – 360.31

Category **:** Filler and diluent

Description:

White to off white or creamy white crystalline particles or powder, odourless, sweet tasting.

Solubility:

Freely soluble in water, practically insoluble in chloroform, ethanol and ether.

Stability and Storage:

Store in a well-closed container to prevent absorption of moisture and odours. Under humid conditions mold growth may occur. Lactose may develop

brown colouration on storage. This reaction is accelerated by warm-damp conditions.

Safety:

Adverse reactions to lactose is largely attributed to lactose intolerance, which occurs in persons with a deficiency of the intestinal enzyme lactose.

6. MATERIALS AND METHODS

6.1.1 Materials used

The following materials that were either AR/LR grade or the best possible pharma grade available were used as supplied by the manufacturer

Sr. No.	Materials	Suppliers
1.	Clarithromycin	Microlabs Ltd. Hosur
2.	HPMC K4M	Microlabs Ltd. Hosur
3.	HPMC K15M	Microlabs Ltd. Hosur
4.	Chitosan	Microlabs Ltd. Hosur
5.	Sodium bicarbonate	Microlabs Ltd. Hosur
6.	Lactose (Monohydrate)	Microlabs Ltd. Hosur
7.	Magnesium Stearate	Microlabs Ltd. Hosur
8.	Hydrochloric Acid	Microlabs Ltd. Hosur

6.1.2 Detailed Of instrument used

1.	Electronic Balance	Shimadzu ELB-300
2.	Hardness Tester	Swastik
3.	Friability test apparatus	Roche Friabilator
4.	Hydraulic Press	Kimaya Engineers
5.	Dial Caliper	Mitutoyo, Japan.
6.	Tablet Dissolution Tester (USPXX III)	Lab India, Lambda 25
7.	Tap Density Tester	Lab India, Lambda 25
8.	UV Spectrophotometer	Lab India, Lambda 25
9.	FTIR Spectrophotometer	Cat j. shimadzu

6.2 Preformulation Studies

It is one of the important prerequisite in development of any drug delivery system.preformulation studies were performed on the drug, which included solubility, melting point, Flow properties,compatibility studies.

a) Solubility

Solubility of Clarythromycin was determined in ethanol (95%), Chloroform, acetone,ether,and 0.1 N HCL.Solubility studies were performed by taking excess amount of Clarythromycin in different beakers containing the solvent. The mixture were shaken for 10 hrs at regular intervals. The solution were filtered by using Whatmanns filter paper grade no 41. The filtered solution were analysed Spectrophotometrically.

b) Melting point

Melting point of the clarythromycin was determined by capillary method.

c) Flow properties

a) Angle of Repose (θ):

The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

The granules were allowed to flow through the funnel fixed to a stand at definite height (H). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$\tan \theta = h/r$

$\theta = \tan^{-1} (h/r)$

where θ = angle of repose

h = height

r = radius

b) Compressibility Index:

The flowability of powder can be evaluated by comparing the bulk density (Do) and taped density (Df) of powder and the rate at which it packed down.

Compressibility index is calculated by –

$$\text{Compressibility index (\%)} = \frac{Df - Do}{Df} X\ 100$$

Where

Do = Bulk density

Df = Tapped density

c) Compatibility Studies:

They provide framework for the drug in combination with the excipients in the fabrication of the dosage form and establish that active drug has not undergone degradation. This can be confirmed by carrying out infrared light absorption scanning spectroscopy.

I.R. Studies:

It is one of the most powerful analytical technique for chemical identification of drug.

Method:- The pure drug and its formulation were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed

6.2.1 Preparation of Standard Calibration Curve:[68]

The calibration curve was obtained by dissolving Clarithromycin in 0.1N

Hydrochloric acid and further dilutions were made using 0.1N Hydrochloric acid and absorbance measured spectrometrically at 203nm. Beer's Law was obeyed in the concentration range of 20-120μg/ml.

Method:

Standard stock solution:-

The stock solution was freshly prepared by weighing specified amount of Clarithromycin in 100ml volumetric flask. The drug was dissolved in and diluted to volume with 0.1N hydrochloric acid.

Preparation of Calibration Curve:-

The aliquots of standard solution were taken in a series of 50ml of volumetric flasks. The mixtures were properly shaken. The resulting samples were ready to form the calibration curve.

The absorbance values were measured at 203nm against reference blank, plotted against concentration to obtain the standard calibration curve.

6.2.2. Formulation of Hydrodyamically Balanced Tablets:

Floating matrix tablets containing Clarithromycin were prepared by direct compression technique using varying concentrations of different grades of polymers with sodium bicarbonate.

All the ingredients except magnesium stearate were blended in glass mortar uniformly. After sufficient mixing of drug as well as other components, magnesium stearate was added and further mixed for additional 2-3 minutes. The tablets were compressed with 13mm punch using hydraulic press. The weight of the tablets was kept constant for formulations F1 to F10. The composition of all formulations was given in Table 1.

6.2.3 Evaluation of Hydrodynamically Balanced Tablets:

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

6.2.4 Evaluation of granules

a) Angle of Repose (θ):

The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

The granules were allowed to flow through the funnel fixed to a stand at definite height (H). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$\tan \theta = h/r$

$\theta = \tan^{-1} (h/r)$

where θ = angle of repose

h = height

r = radius

b) Compressibility Index:

The flowability of powder can be evaluated by comparing the bulk density (Do) and taped density (Df) of powder and the rate at which it packed down.

Compressibility index is calculated by –

$$\text{Compressibility index (\%)} = \frac{Df - Do}{Df} X\ 100$$

Where

Do = Bulk density

Df = Tapped density

6.2.5 Evaluation of tablet

a) Shape of Tablets:

Directly compressed tablets were examined under the magnifying lens for the shape of the tablet.

b) Tablet Dimensions:[71]

Thickness and diameter were measured using a calibrated dial caliper. Three tablets of each formulations were picked randomly and thickness was measured individually.

C) Thickness

The dimensions of the tablet like thickness, length were measured using vernier-calipers. Ten tablets were selected randomly for this test and the average value was reported.

d) Hardness:[71]

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets were determined using Monsanto hardness tester. It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the same tablets from each tablets was determined.

e) Friability test:

The friability of tablets were determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (Winitial) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (Wfinal). The % friability was then calculated by –

$$F = \frac{W\ initial - W\ final}{W\ initial} \times 100$$

% Friability of tablets less than 1% are considered acceptable.

f) Weight Variation Test:[71]

Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation is allowed in the weight of a tablet by U.S. Pharmacopoeia. The following percentage deviation in weight variation is allowed.

In all formulations, the tablet weight is more than 324mg, hence 5% maximum difference allowed.

Average weight of a tablet	Percentage deviation
130 mg or less	10
>130mg and <324mg	7.5
324 mg or more	5

g) Test for Content Uniformity:[68]

Tablet containing 500mg of drug is dissolved in 100ml of 0.1N HCl taken in volumetric flask. The drug is allowed to dissolve in the solvent. The solution was filtered, 1ml of filtrate was taken in 50ml of volumetric flask and diluted up to mark with 0.1N HCl and analysed spectrophotometrically at 203nm. The concentration of Clarithromycin in mg/ml was obtained by using standard calibration curve of the drug. Claimed drug content was 500mg per tablet. Drug content studies were carried out in triplicate for each formulation batch.

h) Tablet Density:[73]

Tablet density is an important parameter for floating tablets. The tablet will only float when its density is less than that of gastric fluid (1.004). The density was determined using following relationship.

$V = \pi r^2 h$

$d = m/v$

v = volume of tablet (cc)

r = radius of tablet (cm)

h = crown thickness of tablet (g/cc)

m = mass of tablet

i) Buoyancy / Floating Test:[74]

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

j) Swelling Study:[75]

The swelling behaviour of a dosage form is measured by studying its weight gain or water uptake. The dimensional changes can be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake is measured in terms of percent weight gain, as given by the equation.

$$WU = \frac{W1 - W0}{W0} \times 100$$

Wt = Weight of dosage form at time t.

W0 = Initial weight of dosage form

k) Effect of hardness on Buoyancy Lag Time (BLT) or Floating Lag Time (FLT):[77]

Formulation F2 was selected to study the effect of hardness on buoyancy lag time. The tablets of batch F2 were compressed at three different compression pressures to get the hardness of 5kg/cm2, 7kg/cm2 and 9kg/cm2. The tablets were evaluated for Buoyancy Lag Time. The method followed is same as that of Buoyancy test.

l) In-vitro Dissolution Study:-[76]

In-vitro release studies were carried out using USP XXIII dissolution test apparatus. 900ml of 0.1N HCl (pH 1.2) was filled in dissolution vessel and the temperature of the medium was set at $37^0C \pm 0.10^0C$. For the study ring/mesh assembly was used. The tablet was put inside the ring assembly and placed inside the dissolution vessel. The speed was set at 50 rpm. 1ml of sample was withdrawn at predetermined time intervals for 10 hours and same volume of fresh medium was replaced. The samples were analyzed for drug content against 0.1N HCl as a blank at λmax 203nm using U.V. spectrophotometer.

m) Curve fitting analysis:

The mechanism of Clarithromycin released from the matrix system was studied by fitting the dissolution data obtained to following equation.

1. Korsmeyer – Peppas equation
2. Zero order equation
3. Higuchi square root equation

n) Comparison with commercial marketed product:

The promising formulation was compared with marketed product formulation by checking various physicochemical parameters.

o) Stability study

The optimum formulation was tested for a period of 12 weeks at 40c with 75% RH for drug content and other parameters.

7. RESULTS AND DISCUSSION

7.1 EXPERMENTAL METHODS

FORMULATION AND EVALUATION OF CLARYTHROMYCIN FLOATING TABLETS:

All the formulations were prepared by direct compression method using different polymers. (designated as F-1 to F-10).

PROCEDURE: DIRECT COMPRESSION

1. Clarythromycin and all other ingredients were individually passed through sieve ≠ 60.
2. All the ingredients were mixed thoroughly by triturating up to 15 min.
3. The powder mixture was lubricated with talc,Magnesium stearate.
4. The tablets were prepared by using direct compression method.

7.1.1 Preformulation studies

Hydrodynamically balanced tablets of Clarithromycin were prepared and evaluated for their use as gastroretentive drug delivery systems to increase its local action and bioavailability

In the present work total Ten formulations were prepared and complete composition of all batches shown in Table4. The tablets were then characterized for various physicochemical parameters.

Table No:1 preformulation Studies

S.No.	Characteristics	Results
1.	Physical state	White to off white crystalline powder odourless
2.	Solubility Analysis	Insoluble (342mg/lit)
3.	Bulk density	1.18 g/cm3
4.	Tap density	0.221g/ml
5.	Compressibility index	41.11%
6.	Residue on ignition	1% max
7.	pH	8-10
8.	Optical rotation	89^0 -95^0
9..	Loss on drying	3% max
10	Melting point	220^0C

7.1.2. COMPATIBILITY STUDY:

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied.

The characteristic absorption peaks of Clarithromycin were obtained at 891.60cm-1, 1049.30cm-1, 1373.95cm-1, 1691.72cm-1.

The peaks obtained in the spectras of each formulation correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components. The spectras for all formulations are shown in Fig. 12 to Fig. 14.

FIG. 12 : I.R. SPECTRA FOR CLARITHROMYCIN

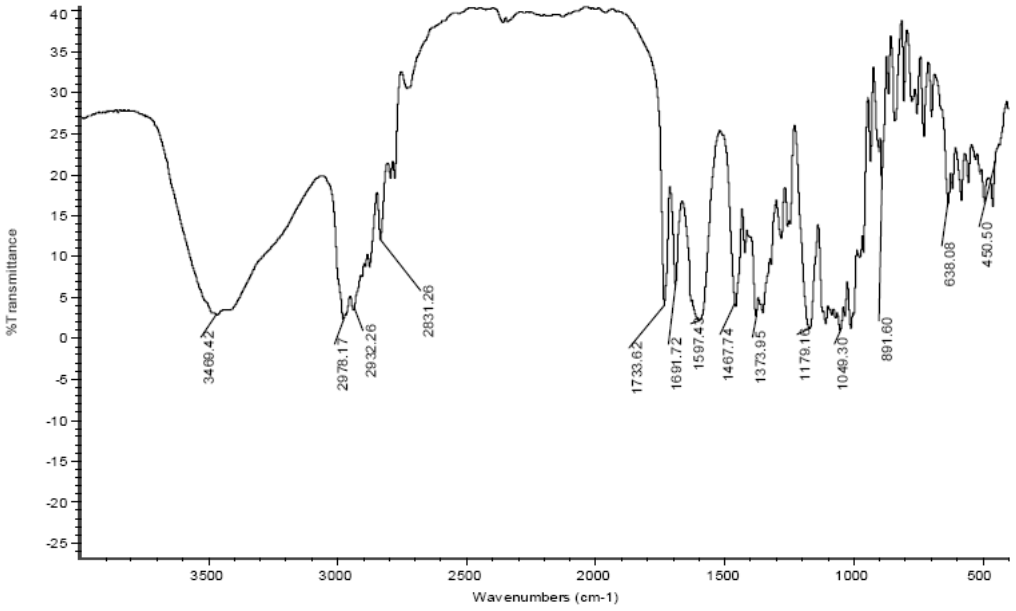


Fig.13: I.R SPECTRA OF HPMC K15M

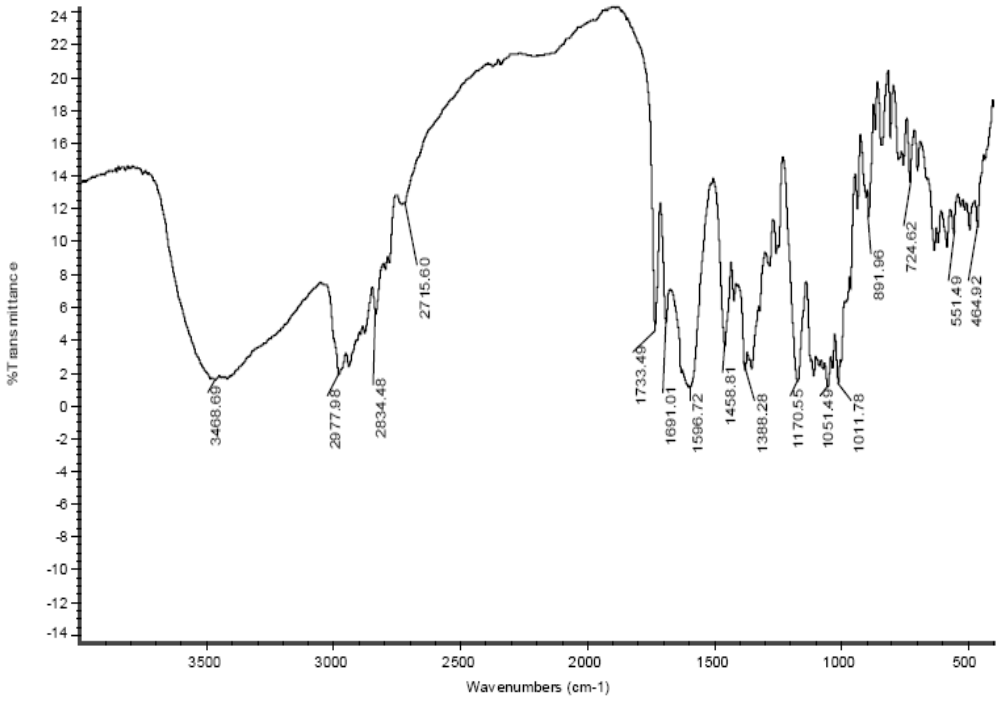


Fig.14: I.R. INTERPRETATION OF PHYSICAL MIXTURE

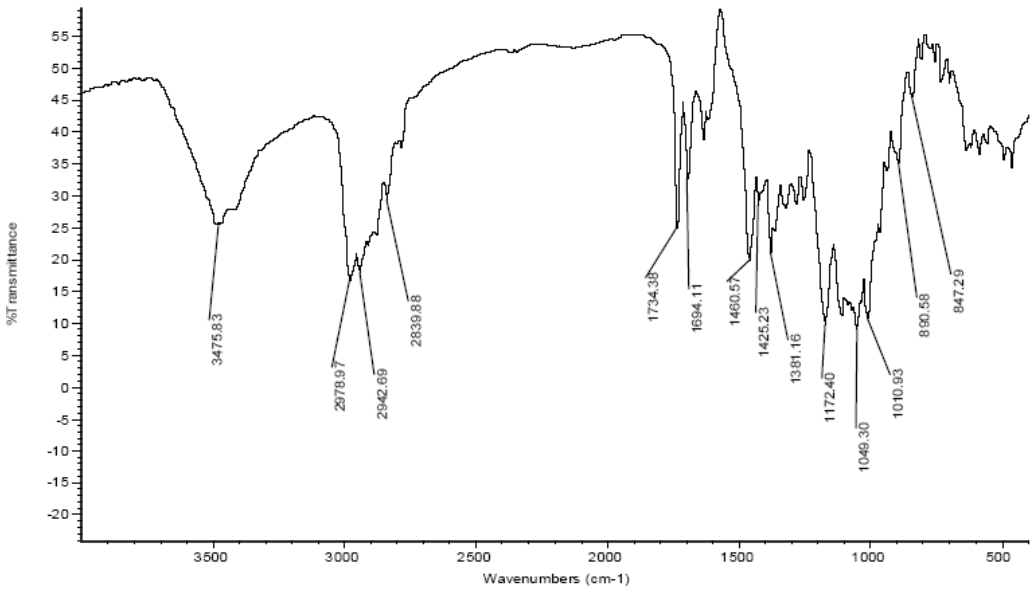


Table No 2: Characteristic peaks In FTIR spectra of Clarithromycin

Wave number in cm^{-1}	Functional groups	Pure drug Clarithromycin	Physical mixture
700-900	C-H Bending	891.60 cm^{-1}	890.58 cm^{-1}
1020-1070	C-O Stretching	1049.30 cm^{-1}	1049.30 cm^{-1}
1350-1480	-C-H Bending	1373.95 cm^{-1}	1381.16 cm^{-1}
1640-1690	C=O Stretching	1691.72 cm^{-1}	1694.11 cm^{-1}
2500-3300	O-H Stretching	2978.17 cm^{-1}	2978.17 cm^{-1}

7.2. STASTANDARD CALIBRATION CURVE:

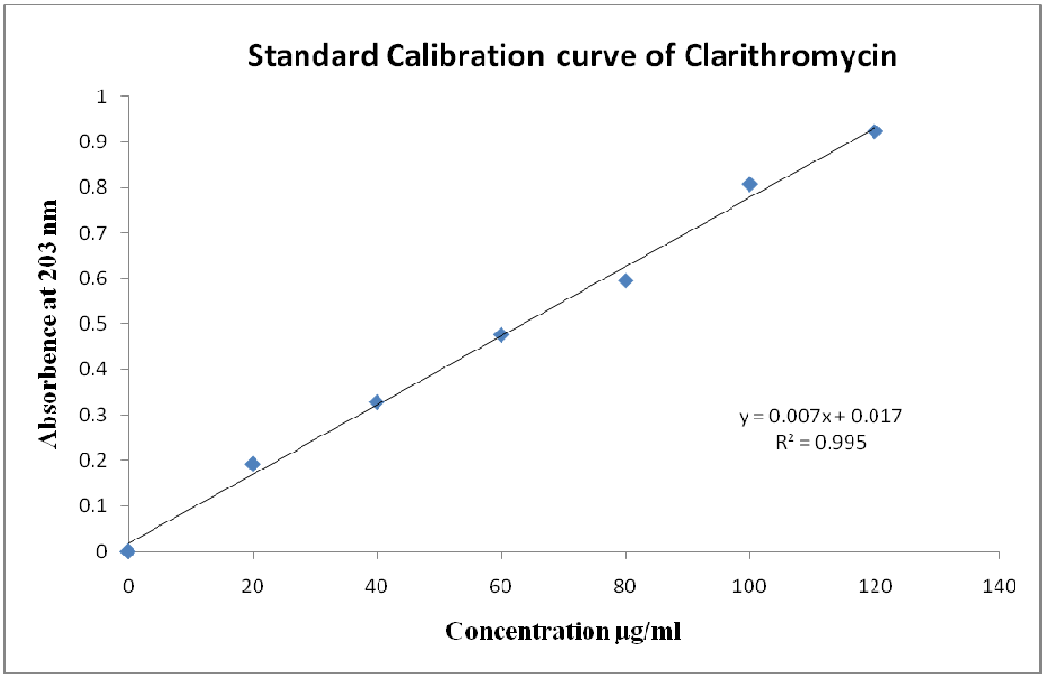
Standard calibration curve of Clarithromycin was drawn by plotting absorbance V/s concentration. The max of Clarithromycin in 0.1N HCl was determined to be 203 nm as shown in Fig.15. The absorbance values are tabulated in

Table3. Standard calibration curve of Clarithromycin in the Beer's range between 20-120 µg/ml .

Table No3: Standard Calibration Curve of Clarithromycin at 203nm by UV Spectrometry

Sl. No.	Concentration (g/ml)	Absorbance
1.	20	0.192
2.	40	0.328
3.	60	0.476
4.	80	0.595
5.	100	0.807
6.	120	0.923

Fig.15: Standard Calibration Curve of clarythromycin



7.3 Formulation of CiarithromycinTablet (in mgs)

Table No4: formulation of Hydrodynamically Balanced Tablets of Clarithromycin (in mgs)

Ingredients(in mgs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Clarithromycin	500	500	500	500	500	500	500	500	500	500
HPMC K 4 M	200	-	-	-	100	100	100	-	-	-
HPMC K 10M	-	200	-	-	100	-	-	100	100	
HPMC K 15M	-	-	200	-	-	100	-	100		100
Chitosan	-	-	-	200	-	-	100		100	100
Sodium bicarbonate	80	80	80	80	80	80	80	80	80	80
Lactose	10	10	10	10	10	10	10	10	10	10
Mag.stearate	10	10	10	10	10	10	10	10	10	10

7.4 EVALUATION OF HYDRODYNAMICALLY BALANCED TABLET FORMULATIONS:

1. Evaluation of granules:

a. ***Angle of Repose (θ):-*** The values obtained for angle of repose for all formulations are tabulated in Table5. The values were found to be in the range from 24.30' to 29.88'. This indicates good flow property of the powder blend.

b. ***Compressibility Index:-*** Compressibility index value ranges between 12.30% to 16.34% indicating that the powder blend have the required flow property for direct compression.

Table No.5: Angle of Repose, Compressibility Index

Batch	Angle of repose	Compressibility index
F1	24.30 ^{o}	12.30
F2	25.41 ^{o}	14.58
F3	26.77 ^{o}	15.67
F4	28.56 ^{o}	16.34
F5	24.72 ^{o}	14.12
F6	25.28 ^{o}	14.48
F7	27.08 ^{o}	14.59
F8	25.63 ^{o}	14.74
F9	28.45 ^{o}	15.34
F10	29.88 ^{o}	15.41

2. Evaluation of tablet:

a) Shape of the tablet:-

Microscopic examination of tablets from each formulation batch showed circular shape with no cracks.

b) Tablet dimensions:-

The dimensions determined for formulated tablets were tabulated in Table6. Tablets mean thickness (n=3) were almost uniform in all the five formulations and were found to be in the range of 5.12mm to 5.18mm. The diameter of the tablet ranges between 12.98mm to 12.99mm.

c)Thickness

The dimensions of the tablet like thickness, length were measured using vernier-calipers. Ten tablets were selected randomly for this test and the average value was reported.

d) Hardness test:-

The measured hardness of tablets of each batch ranged between 4.1 to 4.5kg/cm2 (Table6). This ensures good handling characteristics of all batches.

e) Friability Test:-

The values of friability test were tabulated in Table 6. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

.f) Weight Variation Test:-

The percentage weight variation for all formulations were shown in Table 6. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±5% of the weight. The weight of all the tablets were found to be uniform with low standard deviation values.

g) Drug Content Uniformity:-

The percentage of drug content was found to be between 97.4% to 99.5% of Clarithromycin, which was within acceptable limits. Table 6 showed the results of drug content uniformity in each batch

Table No.6: Physical Properties of Tablets of Batch F1 to F10

Batch	Diameter	thickness	hardness	friability	Weight variation	Drug content
F1	12.99 ±0.04	5.16 ±0.01	4.5 ±0.47	0.41	800.65 ±1.29	97.01
F2	12.98 ±0.01	5.15 ±0.02	4.4 ±0.1	0.40	800.41 ±1.12	98.35
F3	12.98 ±0.006	5.14 ±0.01	4.4 ±0.32	0.36	800.50 ±1.74	99.50
F4	12.98 ±0.07	5.16 ±0.01	4.3±0.42	0.38	800.05 ±1.37	97.40
F5	12.98 ±0.04	5.15 ±0.03	4.2±0.41	0.37	801.10 ±1.13	99.40
F6	12.99 ±0.067	5.12 ±0.06	4.1±0.54	0.38	799.55 ±1.18	98.01
F7	12.98 ±0.05	5.16 ±5.15	4.2±0.32	0.42	799.85 ±1.65	99.21
F8	12.99 ±0.06	5.15 ±0.02	4.3±0.65	0.38	800.03 ±1.11	98.69
F9	12.98 ±0.02	5.16 ±0.03	4.4±0.41	0.39	800.68 ±1.35	98.98
F10	12.98 ±0.056	5.18 ±0.01	4.5±0.35	0.37	801.65 ±1.49	98.40

h) Tablet density:-

To provide good floating behavior in the stomach, the density of the device should be less than that of the gastric contents (1.004g/cm3). All the batches showed density below than that of gastric fluid (1.004). The values are shown in Table7.

When tablet contacts the test medium, tablet expanded (because of swellable polymers) and there was liberation of CO_2 gas (because of effervescent agent, $NaHCO_3$). The density decreased due to this expansion and upward force of CO_2 gas generation. This plays an important role in ensuring the floating capability of the dosage form.

i) Buoyancy Study:-

On immersion in 0.1N HCl solution pH (1.2) at 37^0C, the tablets floated, and remained buoyant without disintegration. Table 7 shows the results of Buoyancy study & shows Buoyancy character of prepared tablet.

From the results it can be concluded that the batch containing only HPMC polymers showed good Buoyancy lag time (BLT) and Total floating time (TFT).

Formulation F3 containing HPMC K15M showed good BLT of 49 sec, while the formulation containing chitosan alone and in combination with HPMC K15M showed highest BLT, and TFT of less than 12 hrs. This may be due to the amount of polymer and gas generating agent, which were kept constant in the present study. The gas generated cannot be entrapped inside the gelatinous layer, and it escapes leading to variation in BLT and TFT.

Table no.7: Tablet Density, Buoyancy Lag Time, TotalFloatingTime

Batch	**Tablet density**	**Buoyancy lag time (sec)**	**Total floating time(Hrs)**
F1	0.93	62	>12
F2	0.88	54	>12
F3	0.82	49	>12
F4	0.99	134	>6
F5	0.85	58	>12
F6	0.89	55	>12
F7	0.95	125	>7
F8	0.86	118	>12
F9	0.93	107	>9
F10	0.90	102	>10

j) Swelling Study:-

Swelling ratio describes the amount of water that is contained within the hydrogel at an equilibrium and is a function of the network structure, hydrophilicity and ionization of the functional groups.

Swelling study was performed on all the batches for 5 hr. The results of swelling index is given in Table8. While the plot of swelling index against time (hr) is depicted in Fig.16.

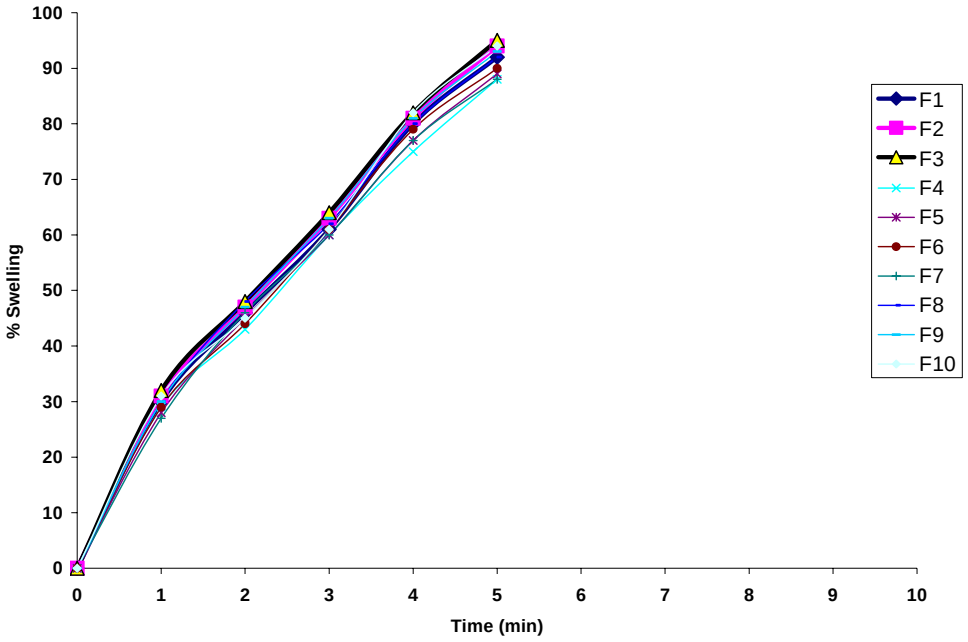
From the results it was concluded that swelling increases as the time passes because the polymer gradually absorb water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates and swells and a gel barrier is formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is repeated towards new exposed surfaces, thus maintaining the integrity of the dosage form.

In the present study, the higher swelling index was found for tablets of batch F3 containing HPMC K15M having nominal viscosity of 15,000 cps. Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as floating capability, hence from the above results it can be concluded that linear relationship exists between swelling process and viscosity of polymer.

Table No.8: Swelling Index of Tablets of Batch F1 to F10

Time in Hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	30	31	32	29	28	29	27	30	30	31
2	46	47	48	43	45	44	46	48	47	45
3	61	63	64	60	60	61	60	62	63	61
4	80	81	82	75	77	79	77	80	81	82
5	92	94	95	88	89	90	88	92	93	94

Fig. No. 16: Swelling Index



k) Effect of hardness on Buoyancy Lag Time:-

The effect of hardness on buoyancy lag time for batch F3was studied. The results of floating lag time of tablet having hardness of 5kg/cm2, 7kg/cm2 and 9kg/cm2 were 102, 480 and 650 sec respectively as tabulated in Table 9. The plot of floating lag time (sec) V/s hardness (kg/cm2). Batch F3 was selected for the study because it showed buoyancy lag time of 49 sec at hardness of 4kg/cm2.

Buoyancy of the tablet was governed by both the swelling of the hydrocolloid particle on surface when it contacts the gastric fluid which in turn results in an increase in the bulk volume and the presence of internal void space in the dry center of the tablet (porosity). On increasing the hardness of the tablets results in increased buoyancy lag time which might be due to high compression resulting in reduction of porosity of the tablet and moreover, the compacted hydrocolloid particles on the surface of the tablet cannot hydrate rapidly when the tablet reaches the gastric fluid and as a result of this, the capability of the tablet to float is significantly reduced.

Table No.9: Effect of Hardness on Buoyancy Lag Time of Batch F3

Hardness in kg/cm^2	**Buoyancy Lag Time (sec)**
4kg/cm^2	49
5kg/cm^2	102
7kg/cm^2	480
9kg/cm^2	650

l) In-vitro Dissolution Study:-

The in-vitro drug release profile of tablet from each batch (F1 to F10) were shown in Table10. The plot of % cumulative drug release V/s time (hr) was plotted and depicted as shown in Fig.17.

For in-vitro dissolution study ring mesh device was used. The reason is that when paddle apparatus is used, the tablets would rise and eventually stick to the flange of the rotating shaft resulting in partial surface occlusion. In case of basket apparatus, it ensures full exposure of all surfaces of hydrophilic swelling tablets that may stick to bottom of dissolution vessel if paddle apparatus was used. However, it was observed that after 5-7 hr the tablets had swollen to such an extent that they were completely constricted by the radius of the basket and completely filled the bottom of the basket. Once the dosage forms completely fills the basket, tablet is unable to swell further and move in unimpeded fashion leading to limited drug release. In order to overcome these drawbacks ring mesh device is employed in the study.

From the in-vitro dissolution data it was found that formulation F4 containing chitosan alone released 97.2% of drug within 6 hr of the study indicating that the polymer amount is not sufficient to control the drug release.

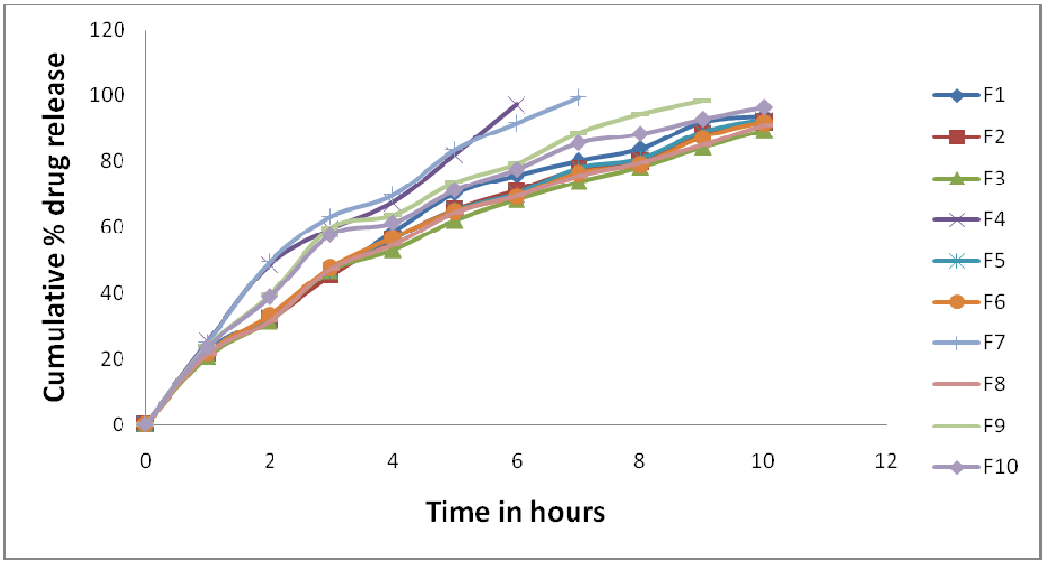
Formulation F3 containing HPMC K15M showed better control of drug release than chitosan alone, and released 96.3% drug at the end of 10 hr. Tablet of batch F1, F2 and F3 contained same amount of polymer of different grades viz. HPMC K4M, HPMC K15M and combination of HPMC K4M and K15M which showed drug release rate of 93.6%, 92.1% and 89.3% respectively. Out of all the ten

formulations batch F3 showed better control over drug release indicating that the release was decreased when the viscosity of the polymer was increased.

Table No.10: Cumulative % Drug Released from Tablet Formulations F1 to F10.

Time in Hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	22.51	21.64	20.70	25.24	21.96	21.64	24.94	21.45	23.73	23.41
2	32.43	31.97	31.54	48.67	32.65	33.34	49.57	31.52	39.47	38.72
3	45.56	45.35	46.87	59.43	47.24	47.72	63.27	47.28	59.84	57.62
4	58.53	56.59	53.12	67.56	56.57	56.78	69.81	54.58	63.71	61.28
5	70.20	65.41	62.14	81.98	65.12	64.84	83.53	64.39	73.59	71.17
6	75.67	71.28	68.45	97.24	70.24	69.38	91.75	69.47	79.28	77.47
7	80.12	77.67	73.85		77.98	76.51	99.42	75.52	88.69	85.53
8	83.76	80.12	78.34		80.79	79.20		79.47	94.35	88.26
9	91.89	88.43	84.35		88.97	87.36		84.91	98.43	92.74
10	93.65	92.11	89.43		92.64	91.95		90.93		96.31

Fig.17: In Vitro drug release plot for Formulation F1-F10



m) Curve Fitting Analysis:-

The results of dissolution data fitted to various drug release kinetic equations. Peppas model was found to be best fitted in all dissolution profile having higher correlation coefficient (r value) followed by Higuchi model and Zero Order Release equation. The kinetic values obtained for different formulations are tabulated in Table11.

Korsemeyer-Peppas model indicates that release mechanism is not well known or more than one type of release phenomena could be involved. The 'n' value could be used to characterize different release mechanisms as:

n	Mechanism
0.5	Fickian diffusion (Higuchi Matrix)
0.5 < n < 1	Non-Fickian diffusion
1	Case II transport

The results are reported in Table 9 and in the present study 'n' value ranges between 0.64 to 0.76 for all ten batches. It ranges between 0.5 to 1, so it was concluded that the drug release occurred via non-Fickian diffusion, which shows that the release from initially dry, hydrophilic glassy polymers that swell when added to water and become rubbery show anomalous diffusion as a result of the rearrangement of macromolecular chains.

7.5 PHARMACOKINETIC STUDIES

Kinetic plots of formulation F3

Fig.18 : Zero order plot

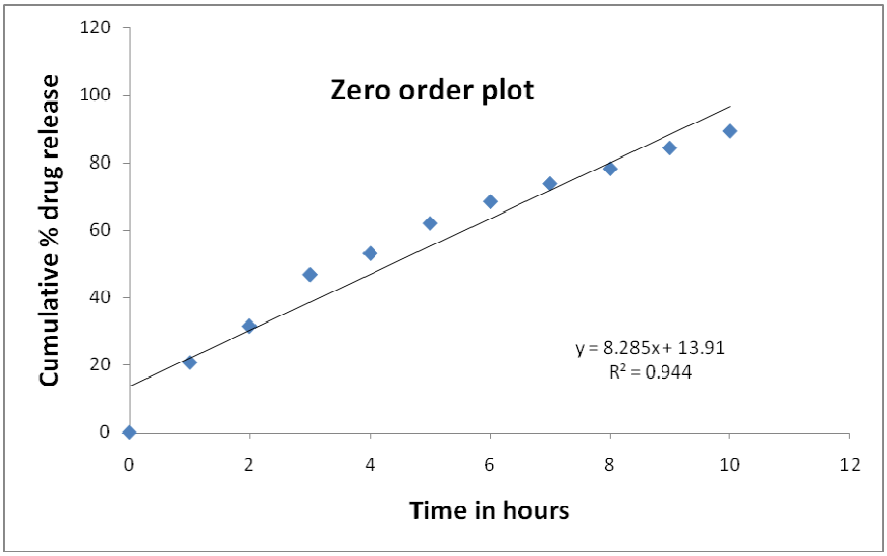


Fig. 19: First order plot

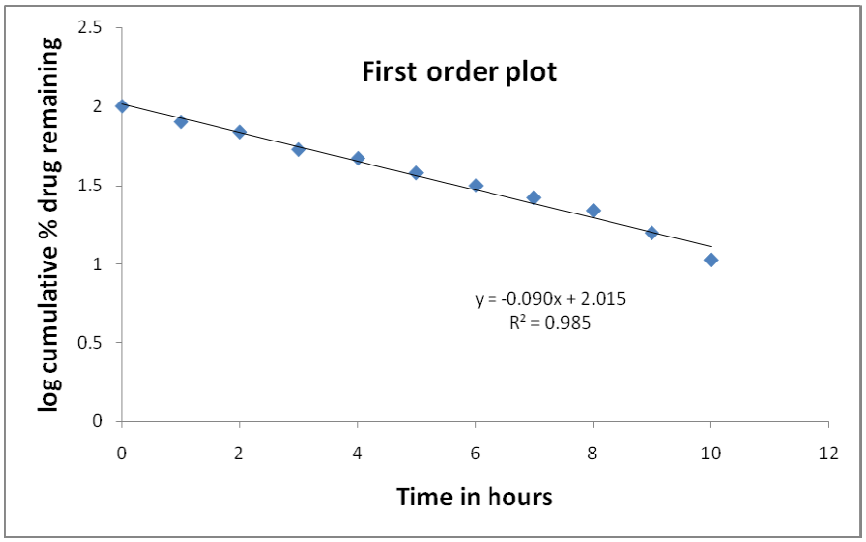


Fig. 20: Higuchi plot

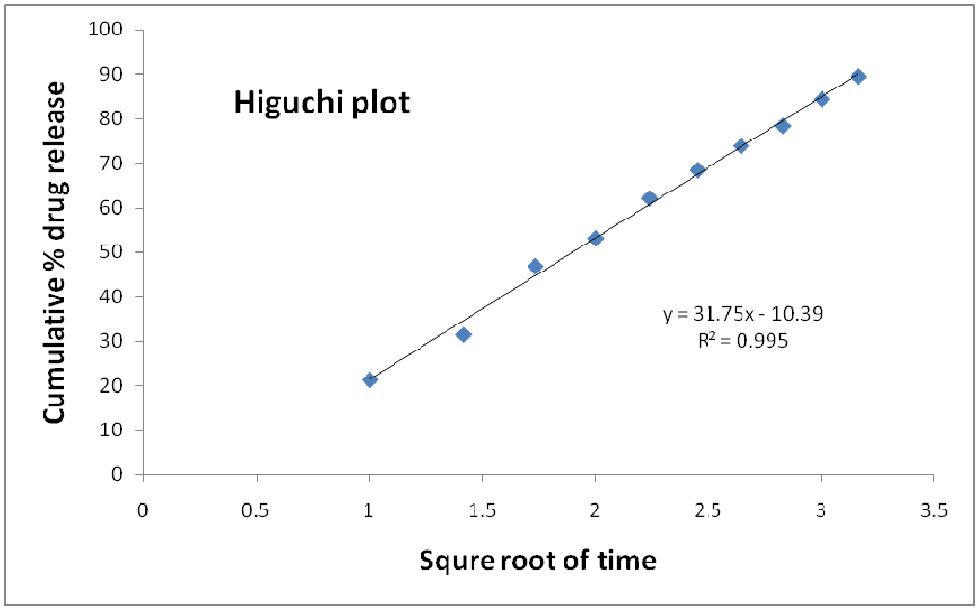


Fig. 21: Korsmeyer peppas plot

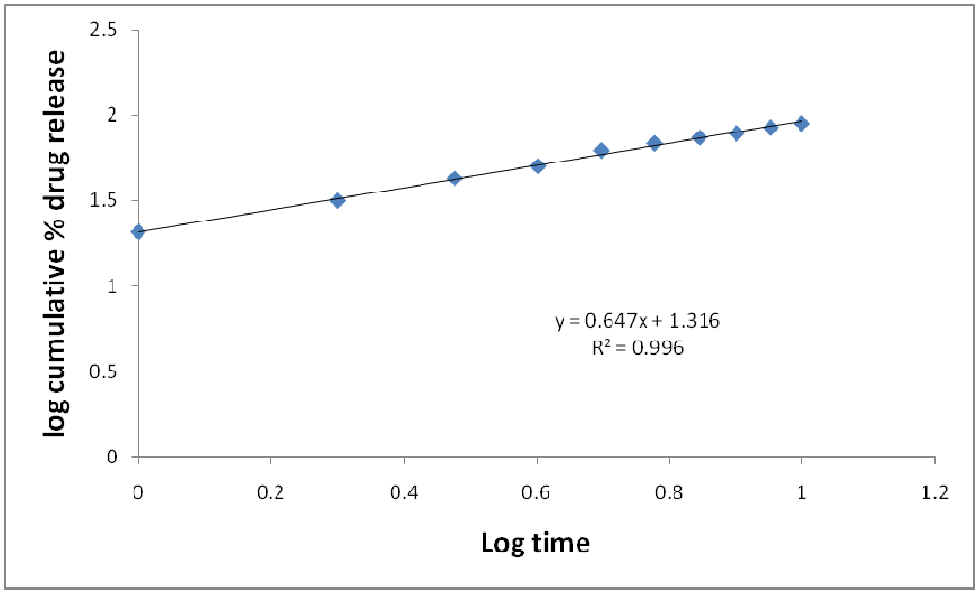


Table No.11:Kinetic Values Obtained From F3 plot Formulation

Formulation	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer -Peppas R^2	n	Best fit model
F3	0.944	0.985	0.955	0.996	0.647	Peppas

7.6 Comparison with Commercial Marketed Product:-

The promising formulation (F3) as found by evaluation studies was compared with marketed product Clarithro ER (500mg). The evaluation parameters tested and compared were drug content uniformity and in-vitro dissolution profile. The values obtained for in vitro dissolution study are recorded in Table no 8.

The mean value of drug content uniformity observed was 99.28%. The marketed product gave 92.31% of drug release in 10 hrs of dissolution study. In-vitro dissolution profile of marketed product in comparison to the formulated batches were shown graphically in Fig 22 and showed that the formulation F3 with 89.4% of drug release has better control over release of drug in comparison to marketed product.

Table No:12 Comparison of Optimization formulation F3 with marketed product

Time in Hrs	F3	Marketed product
1	20.70	24.31
2	31.54	34.25
3	46.87	48.63
4	53.12	59.47
5	62.14	66.65
6	68.45	74.74
7	73.85	78.96
8	78.34	81.94
9	84.35	90.70
10	89.43	92.31

Fig. 22: A Plot for comparison between optimized formulation F3 with Marketed product

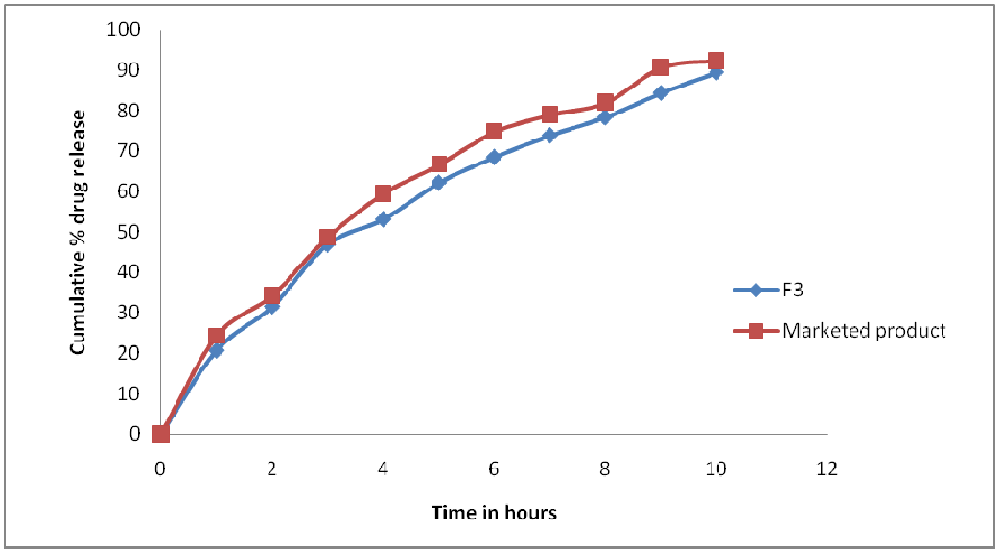


Table no:13 Kinetic studies of optimum formulation F3

Time in hours	√ T	Log T	Cumulative % drug release	Cumulative % drug remain	Log cumulative % drug release	Log cumulative % drug remain
0	0	0	0	100	0	2
1	1.0	0	20.70	79.3	1.315	1.899
2	1.414	0.301	31.54	68.46	1.498	1.835
3	1.732	0.477	46.87	53.13	1.670	1.725
4	2.0	0.602	53.12	46.88	1.725	1.670
5	2.236	0.698	62.14	37.86	1.793	1.578
6	2.449	0.778	68.45	31.55	1.835	1.498
7	2.645	0.845	73.85	26.15	1.868	1.417
8	2.828	0.903	78.34	21.66	1.893	1.335
9	3.0	0.954	84.35	15.65	1.926	1.194
10	3.162	1.0	89.43	10.57	1.951	1.024

7.7 STABILITY STUDIES OF FLOATING TABLETS OF CLARYTHROMYCIN

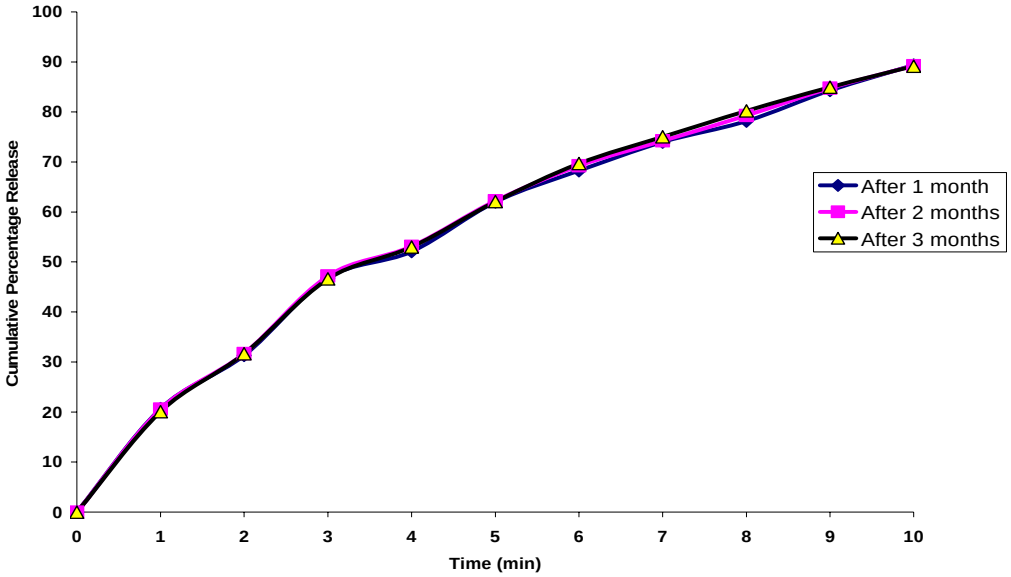
Table No:14 CHARACTERISTICS OF OPTIMIZED TABLET

	Drug Content (%) ± SD	Hardness (Kg/cm^2) ± SD	Floating behaviour	
			Floating lag time (sec)	Floating duration (hrs)
After one month	89.24 ±0.029	4.4 ± 0.32	49	13
After two months	89.04 ±0.024	4.5 ± 0.43	52	13
After three months	88.87 ±0.025	4.56 ± 0.36	58	12

Table No.:15 *IN-VITRO* DRUG RELEASE STUDY

Time (in hours)	Cumulative drug release after one month	Cumulative drug release after two months	Cumulative drug release after three months
0	0.000	0.00	0.00
1	20.67	20.57	20.07
2	31.34	31.68	31.64
3	46.80	47.20	46.60
4	52.08	53.12	53.01
5	62.01	62.23	62.07
6	68.25	69.23	69.68
7	73.98	74.20	75.03
8	78.18	79.28	80.20
9	84.30	84.75	84.93
10	89.43	89.38	89.33

Fig.23: In Vitro Drug Release Study



The tablets were investigated at 40^{o}C/75%RH For 3 months.From the data, The Formulation is found to be stable under the conditions mentioned before since there was no significant change in the percentage amount of drug content and drug release. Thus, it was found that the Fioating tablets of clarithromycin (F3) were stable under these conditions at least for three months.

8. SUMMARY AND CONCLUSION

In the present study Gastroretentive delivery systems of Clarithromycin were successfully developed in the form of Hydrodynamically Balanced Tablets to improve the local action and ultimately its bioavailability.

The tablets were formulated using different grades of polymers (HPMC K4M, HPMC K15M and Chitosan) and effervescing agent (NaHCO3).

IR spectra studies revealed that the drug and the polymers used were compatible. The evaluation parameters like hardness, friability and content uniformity were within the limits for various batches formulated.

Buoyancy lag time, Total floating time, tablet density, Swelling studies showed satisfactory results for batch F1, F2, F3, F5, F6 and F8. The formulation F3 was evaluated for effect of hardness on floating lag time, and the results showed that the floating lag time increased as hardness increased due to reduction in porosity.

In-vitro dissolution of batch F3 containing HPMC K15M showed good drug release rate in comparison to remaining batches containing chitosan, HPMC K4M, HPMC K10M which were not able to sustain their release up to 10 hrs. Formulations subjected to curve fitting analysis showed to best fit Korsemeyer – Peppas equation and followed non-Fickinian diffusion mechanism.

Comparison study with marketed product Clarithro ER showed that the optimized formulation F3 has better control over release rate in comparison with the marketed product.

Hence it was concluded that formulation F3 containing HPMC K15M showed better controlled drug release rate in comparison to other polymers and showed that the release decreases as the viscosity of the polymer increases.

From the findings obtained, it can be concluded that:-

- Hydrodynamically Balanced Tablets of an antibacterial drug Clarithromycin can be formulated as an approach to increase gastric residence time and thereby improve its bioavailability.

- Among the polymers used to improve the gastric residence, cellulose polymers HPMC K4M, HPMC K15M showed better control over drug release in comparison to polysaccharide polymer Chitosan.

- Formulated tablets gave satisfactory results for various physicochemical evaluation for tablets like Tablet dimensions, Hardness, Friability, Weight variation, Tablet density, Swelling index and Content uniformity.

- Overall, tablets of batch F3 possessed quick buoyancy lag time and good total floating time.

- Variation on hardness on tablet of batch F3 was found to effect the floating lag time of the tablet as hardness increased.

- In-vitro release rate showed that the drug release was better controlled in formulation F3 shows better control drug release in comparision to other formulation.

- Formulated floating tablets best fitted to Peppas model followed by Higuchi model and Zero order rate kinetics.

- Formulation F3 has better Sustained drug release in comparison to marketed product Clarithro ER.

- The present work can be continued further to prove its stability during shelf life, *in-vivo* gastric residence time by using gamma scintigraphy and establishment of in vitro – *in vivo* correlation.

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